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(54) Title: USE OF 2-OXO-1-PYRROLIDINE DERIVATIVES FOR THE PREPARATION OF A DRUG

(57) Abstract: The present invention relates to the use of 2-oxo-1-pyrrolidine derivatives (and in particular (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide) for the preparation of drugs for the curative and/or prophylactic treatment of dyskinesia

USE OF 2-OXO-1-PYRROLIDINE DERIVATIVES FOR THE PREPARATION OF A DRUG

The present invention relates to the use of 2-oxo-1-pyrrolidine derivatives (and in particular (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the preparation of drugs for the curative and/or prophylactic treatment of movement disorders or dyskinesia.

Movement and other disorders due to dysfunction of the basal ganglia and related brain structures are of major socio-economic importance. Such disorders can occur as a consequence of inherited or acquired disease, idiopathic neurodegeneration or they may be iatrogenic. The spectrum of disorders is very diverse, ranging from those associated with poverty of movement (akinesia, hypokinesia, bradykinesia) and hypertonia (e.g. Parkinson's disease) to the involuntary movement disorders (hyperkinesias or dyskinesias e.g. Huntington's disease, L-DOPA-induced dyskinesia, tardive dyskinesia , progressive supernuclear palsy , multiple system atrophy , corticobasal degeneration , Wilson's disease , progressive pallidal atrophy).

Parkinson's disease and related conditions represent one of the most prevalent diseases associated with poverty of movement. Parkinsonian symptoms manifest as a syndrome of symptoms characterised by slowness of movement (bradykinesia), rigidity and / or tremor. Parkinsonian symptoms are seen in a variety of conditions, most commonly in idiopathic parkinsonism (i.e. Parkinson's Disease) but also following treatment of schizophrenia (i.e. neuroleptic induced parkinsonism), exposure to toxins/drugs and head injury.

It is widely appreciated that the primary pathology underlying Parkinson's disease is degeneration, in the brain, of the dopaminergic projection from the substantia nigra to the striatum. This has led to the widespread use of dopamine-replacing agents (e.g. L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine agonists) as symptomatic treatments for Parkinson's disease . Such treatments have been successful in increasing the quality of life of patients suffering from Parkinson's disease. However, dopamine–replacement treatments do have limitations, especially following long-term treatment. Problems can include fluctuations (e.g. "on-off " phenomenon , wearing–off of the anti-parkinsonian efficacy of the treatment) and the appearance of a range of side-effects which manifest as abnormal involuntary movements, such as dyskinesias.

Dyskinesias, as a whole, are characterised by the development in a subject of abnormal involuntary movements. One way in which dyskinesias may arise is as a side effect of dopamine replacement therapy for parkinsonism or other basal ganglia-related movement disorders.

Many attempts have been made to identify agents that will prevent the development of, and/or treat dyskinesias although such attempts have met with limited success. There is therefore, a need to discover ways by which movement disorders and dyskinesias may be treated.

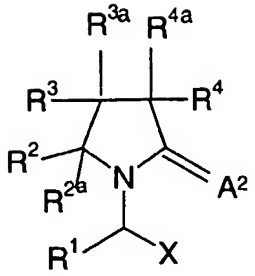
The use of levorotatory (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide, also known as levetiracetam [International Nonproprietary Name] as a protective agent for the treatment and prevention of hypoxic and ischaemic type aggressions of the central nervous system is described in the European patent EP-A-0162 036. That compound can also be employed in the treatment of epilepsy, a therapeutic indication for which it has been demonstrated that its dextrorotatory enantiomer, (R)-(+)-α-ethyl-2-oxo-1-pyrrolidine-acetamide, is completely devoid of activity (A. J. GOWER et al., Eur. J. Pharmacol., 222, (1992), 193-203). That compound has also been described in European patent EP-A-0 645 139 for the treatment of anxiety.

EP-A-162 036 cited above also describes methods for preparing (S)-(-)-α-ethyl-2-oxo-1-pyrrolidine-acetamide which require the synthesis of a starting reactant obtained by resolution of the corresponding racemate. British patent GB-A-2 225 322 describes a method for preparing that compound which offers the advantage of using a natural amino acid which already has the desired stereochemical configuration as the starting material, thus dispensing with any laborious separation of the enantiomers.

2-oxo-1-pyrrolidine derivatives are described in the international patent application WO 01/62726 as well as their use as pharmaceuticals. The derivatives are particularly suited for treating neurological disorders such as epilepsy.

In continuing its research on these compounds, the Applicant has now discovered that (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and also 2-oxo-1-pyrrolidine derivatives possess therapeutic properties which render it particularly useful in the treatment and prophylaxis of movement disorders and dyskinesia.

The present invention thus concerns the use of an active compound which is a 2-oxo-1-pyrrolidine derivatives having the formula II or a pharmaceutically acceptable salt thereof,



(II)

wherein

X is $-CA^1NR^5R^6$ or $-CA^1OR^7$ or $-CA^1-R^8$ or CN;

A^1 and A^2 are independently oxygen, sulfur or $-NR^9$;

R^1 is hydrogen, alkyl, aryl or $-CH_2-R^{1a}$ wherein R^{1a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R^2, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;

R^{2a}, R^{3a} and R^{4a} are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;

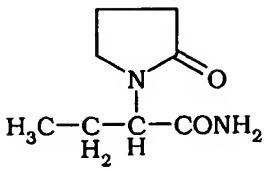
R^5, R^6, $R^7$and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

with the provisos that at least one of as R^2, R^3, R^4, R^{2a}, R^{3a} and R^{4a} is other than hydrogen; and that when the compound is a mixture of all possible isomers , X is $-CONR^5R^6$, A^2 is oxygen and R^1 is hydrogen, methyl, ethyl or propyl then substitution on the pyrollidine ring is other than mono-, di-, or tri-methyl or mono-ethyl; and that when R^1, R^2, R^4, R^{2a}, R^{3a} and R^{4a} are each hydrogen, A^2 is oxygen and X is $CONR^5R^6$ then R^3 is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by an halogen atom;

for the preparation of drugs for the treatment or prophylaxis of dyskinesia.

The present invention concerns also the use of an active compound which is (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide having the formula I



(I)

for the preparation of drugs for the treatment or prophylaxis of movement disorders or dyskinesia.

In a first aspect, the invention concerns the use of the active compound for the manufacture of a medicament for treatment and/or prophylactic treatment of dyskinesia.

The present invention also concerns a method for treating or preventing dyskinesia, comprising administering a therapeutic amount of the active compound, as described above, to a patient. In particular, it concerns a method for treating or preventing movement disorders or dyskinesia, comprising administering a therapeutic amount of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide to a patient in need.

The term "treatment" as used by the Applicant means curative treatment and prophylactic treatment.

By "curative" we mean the efficaciousness of the active compound in treating the current episode.

By "prophylactic" or "maintenance" we mean the prevention of any induction of the recurrence of episodes and the possibility to de-prime the manifestation of dyskinesia .

By "movement disorder", we mean in particular movement disorder associated with a poverty of movement and more particularly to the treatment of parkinsonism, a medical condition characterised by akinesia, hypokinesia or bradykinesia and also conditions characterised by hypertonia. Such disorders include Wilson's disease, progressive supranuclear palsy, and in particular Parkinson's disease and other forms of parkinsonism.

By "dyskinesia" we mean the development in a subject of abnormal involuntary movements. This appears in patients with Huntington's disease, in Parkinson's disease patients exposed to chronic dopamine replacement therapy, and in Schizophrenia patients exposed to chronic treatment with neuroleptics.

The inventors have established that the use of active compounds alone significantly reduces the problems associated with conventional therapies. For instance, side-effects such as abnormal involuntary movements (dyskinesias) induced by conventional therapies do not

develop, or develop to a lesser extent, when active compounds are used in combination with these therapies to treat parkinsonism, schizophrenia and Huntington ' s diseases, and in particular parkinsonism.

The invention is based upon our studies relating to the use of active compounds to alleviate significantly L-DOPA-induced dyskinesias in a non-human primate model of Parkinson's disease.

The 2-oxo-1-pyrrolidine derivatives having the formula II are described in the international patent application WO 01/62726, the content of the application is incorporated by reference.

For the active compounds, in the definitions set forth below, unless otherwise stated, R^{11} and R^{12} are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl, heterocycle or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyl derivative, or sulfinyl derivative, each optionally substituted with any suitable group, including, but not limited to, one or more moieties selected from lower alkyl or other groups as described below as substituents for alkyl.

The term "oxy derivative", as used herein is defined as including $-O-R^{11}$ groups wherein R^{11} is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester, oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocyclooxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative" as used herein, is defined as including $-S-R^{11}$ groups wherein R^{11} is as defined above except for "thio derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

The term "amino derivative" as used herein, is defined as including $-NHR^{11}$ or $-NR^{11}R^{12}$ groups wherein R^{11} and R^{12} are as defined above . Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

The term "acyl derivative" as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula $R^{11}-CO-$, wherein R^{11} is as defined above and may also be hydrogen. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

The term "sulfonyl derivative" as used herein, is defined as including a group of the formula $-SO_2-R^{11}$, wherein R^{11} is as defined above except for "sulfonyl derivative". Non-

limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative" as used herein, is defined as including a group of the formula –SO–R^{11}, wherein R^{11} is as defined above except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-6 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl"). Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, oxyester, oxyamido, heterocycle, vinyl, C1-5-alkoxy, C6-10-aryloxy and C6-10-aryl.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, and 2,2,2-trimethylethyl each optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro and cyano, such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

The term "alkenyl" as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond such as ethenyl (= vinyl), 1-methyl-1-ethenyl, 2,2-dimethyl-1-ethenyl, 1-propenyl, 2-propenyl (= allyl), 1-butenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl, and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle such as mono- and di-halo vinyl where halo is fluoro, chloro or bromo.

The term "alkynyl" as used herein, is defined as including a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (= propargyl), and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle, such as haloethynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight- or branched chains, C1-12, preferably C1-4-alkylene or C2-12-, preferably C2-4-alkenylene or -alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfinyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfinyl, alkylthio, oxyester, oxyamido, aryl, C1-6-alkoxy, C6-10-aryloxy, C1-6-alkyl, C1-6-haloalkyl . Aryl radicals are preferably monocyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl and phenyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula –OH.

The term "thiol", as used herein, represents a group of the formula –SH.

The term "cyano", as used herein, represents a group of the formula –CN.

The term "nitro", as used herein, represents a group of the formula $-NO_2$.

The term "nitrooxy", as used herein, represents a group of the formula $-ONO_2$.

The term "amino", as used herein, represents a group of the formula $-NH_2$.

The term "azido", as used herein, represents a group of the formula $-N_3$

The term "carboxy", as used herein, represents a group of the formula –COOH.

The term "sulfonic acid", as used herein, represents a group of the formula $-SO_3H$.

The term "sulfonamide", as used herein, represents a group of the formula $-SO_2NH_2$.

The term "ester" as used herein is defined as including a group of formula $-COO-R^{11}$ wherein R^{11} is as defined above except oxy derivative, thio derivative or amino derivative.

The term "ether" is defined as including a group selected from C1-50- straight or branched alkyl, or C2-50- straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.

The term "amido" is defined as including a group of formula $-CONH_2$ or $-CONHR^{11}$ or $-CONR^{11}R^{12}$ wherein R^{11} and R^{12} are as defined above.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of

aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl, thieno(2,3-b)furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino , morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) or the same which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2.1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

In the above definitions it is to be understood that when a substituent such as R^2, R^3, R^4, R^{2a}, R^{3a}, R^{4a}, R^5, R^6, R^7, R^8 is attached to the rest of the molecule *via* a heteroatom or a carbonyl, a straight- or branched chain, C1-12-, preferably C1-4-alkylene or C2-12, preferably C2-4-alkenylene or -alkynylene bridge may optionally be interposed between the heteroatom or the carbonyl and the point of attachment to the rest of the molecule.

Preferred examples of X are $-COO\ R^7$ or $-CONR^5R^6$, wherein R^5, R^6 and R^7 are preferably hydrogen, C1-4 -alkyl, phenyl or alkylphenyl.

Preferably X is carboxy or $-CONR^5R^6$, wherein R^5 and R^6 are preferably hydrogen, C1-4 -alkyl, phenyl or alkylphenyl, especially $-CONH_2$.

Preferably A^1 and A^2 are each oxygen.

Preferably R^1 is hydrogen, alkyl, especially C1-12 alkyl, particularly lower alkyl or aryl especially phenyl.

Examples of preferred R^1 groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or ter-butyl, 2,2,2-trimethylethyl each optionally attached *via* a methylene bridge or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl. R^1 as ethyl is especially preferred.

Preferably R^2 and R^{2a} are independently hydrogen, halogen or alkyl, especially lower alkyl.

Examples of preferred R^2 and R^{2a} groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl. Especially at least one and most preferably both of R^2 and R^{2a} are hydrogen.
Preferably R^{3a}, R^4 and R^{4a} are independently hydrogen, alkyl, especially methyl or ethyl or aryl especially phenyl or aralkyl, especially benzyl.

Examples of preferred R^{3a}, R^4 and R^{4a} groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl. Especially at least one and most preferably both of R^4 and R^{4a} are hydrogen.
R^{3a} is particularly hydrogen or alkyl, especially lower alkyl and is most preferably hydrogen.
Preferably R^3 is hydrogen, C1-12-alkyl, especially C1-6-alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato or alkoxy and attached to the ring either directly or *via* a thio, sulfinyl, sulfonyl, carbonyl or oxycarbonyl group and optionally, a C1-4-alkylene bridge, particularly methylene; C2-6-alkenyl or -alkynyl, especially C2-3-alkenyl or -alkynyl each optionally substituted by one or more halogens; azido; cyano; amido; carboxy; triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or piperazinyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or *via* a carbonyl group or a C1-4-alkylene bridge, particularly methylene; naphthyl; or phenyl, phenylalkyl or phenylalkenyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, C1-6-alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4-alkylene bridge, particularly methylene.

Also, preferably, R^3 is C1-6-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato, azido, alkoxy, alkylthio, phenylsulfonyl; nitrooxy; C2-3-alkenyl or -alkynyl each optionally substituted by one or more halogens or by acetyl; tetrazolyl, pyridyl, furyl, pyrrolyl, thiazolyl or thienyl; or phenyl or phenylalkyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* a sulfonyloxy and optionally additionally a C1-4-alkylene bridge, particularly methylene.

Other examples of preferred R^3 groups are hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

R^3 is especially C1-4-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato or azido; C2-5-alkenyl or -alkynyl, each optionally substituted by one or more halogens; thienyl; or phenyl optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl or azido.

Further examples of preferred R^3 groups are C1-6 alkyl and C2-6 haloalkenyl.

Preferably R^5 and R^6 are independently hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl, especially hydrogen or methyl.

Especially at least one and most preferably both of R^5 and R^6 are hydrogen.

Preferably R^7 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or tert-butyl, 2,2,2-trimethylethyl, methoxy, ethoxy, phenyl, benzyl or the same substituted by at least one halogen atom such as trifluoromethyl, chlorophenyl.

Preferably R^7 is hydrogen, methyl or ethyl especially hydrogen.

Preferably R^8 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl, phenyl, benzyl or the same substituted by at least one halogen atom such as trifluoromethyl, chlorobenzyl.

Preferably R^8 is hydrogen or methyl.

Combinations of one or more of these preferred compound groups are especially preferred.

A particular group of compounds of formula II (Compounds 1A) comprises those wherein,

A2 is oxygen;

X is $-CONR^5R^6$ or $-COOR^7$ or $-CO-R^8$ or CN;

R^1 is hydrogen or alkyl, aryl, , halogen, hydroxy, amino, nitro, cyano;

R^2, R^3, R^4, are the same or different and each is independently hydrogen or halogen, hydroxy, amino, nitro, cyano, acyl, acyloxy, a sulfonyl derivative, a sulfinyl derivative, an amino derivative, carboxy, ester, ether, amido, sulfonic acid, sulfonamide, alkoxycarbonyl, a thio derivative, alkyl, alkoxy, oxyester, oxyamido, aryl, an oxy derivative, heterocycle, vinyl and R^3 may additionally represent C2-5 alkenyl, C2-5 alkynyl or azido each optionally substituted by one or more halogen, cyano, thiocyano, azido, , cyclopropyl, acyl and/or phenyl; or phenylsulfonyloxy whereby any phenyl moiety may be substituted by one or more halogen, alkyl, haloalkyl, alkoxy, nitro, amino, and/or phenyl; most preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

R^{2a}, R^{3a} and R^{4a} are hydrogen

R^5, R^6, R^7 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle, alkylthio or thio derivative.

Within these Compounds 1A, R^1 is preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl; most preferably methyl, ethyl or n-propyl.

R^2 and R^4 are preferably independently hydrogen or halogen or methyl, ethyl, propyl, isopropyl, butyl, isobutyl; and, most preferably, are each hydrogen.

R^3 is preferably C1-5 alkyl, C2-5 alkenyl, C2 – C5 alkynyl, cyclopropyl, azido, each optionally substituded by one or more halogen, cyano, thiocyano, azido, alkylthio, cyclopropyl, acyl and/or phenyl; phenyl; phenylsulfonyl; phenylsulfonyloxy, tetrazole, thiazole, thienyl, furyl, pyrrole, pyridine, whereby any phenyl moiety may be substituted by one or more halogen, alkyl, haloalkyl, alkoxy, nitro, amino, and/or phenyl; most preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

X is preferably –COOH or –COOMe or –COOEt or $-CONH_2$; most preferably $-CONH_2$.

A further particular group of compounds of formula II (Compounds 1B) comprises those wherein,

X is $-CA^1NH_2$, $-CA^1NHCH_3$ or $-CA^1N(CH_3)_2$;

R^1 is alkyl or phenyl;

R^3 is alkyl, alkenyl, alkynyl, cyano, isothiocyanato, ether, carboxyl, amido, aryl, heterocycle; or

R^3 is CH_2R^{10} wherein R^{10} is hydrogen, cycloalkyl, oxyester, oxyalkylsulfonyl, oxyarylsufonyl, aminoalkylsulfonyl, aminoarylsulfonyl, nitrooxy, cyano, isothiocyanato, azido, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, heterocycle, aryloxy, alkoxy or trifluoroethyl;

R^{3a} is hydrogen, alkyl or aryl (especially with the proviso that when R^{3a} is hydrogen, R^3 other than methyl);

or R^3R^{3a} form a cycloalkyl;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen.

Within the compounds of formula II,

R^1 is preferably alkyl especially C1-12- more particularly C1-6-alkyl and is most preferably ethyl;

R^2, R^{2a} , R^{3a} and R^{4a} are preferably hydrogen;

R^3 is preferably selected from hydrogen; C1-12-alkyl, especially C1-6-alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato or alkoxy and attached to the ring either directly or *via* a thio, sulfinyl, sulfonyl, carbonyl or oxycarbonyl group and optionally additionally a C1-4-alkylene bridge, particularly methylene; C2-6-alkenyl or –alkynyl, especially C2-3-alkenyl or –alkynyl, each optionally substituted by one or more halogens; azido; cyano; amido; carboxy; triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or piperazinyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or *via* a carbonyl group or a C1-4-alkylene bridge, particularly methylene; naphthyl; or phenyl, phenylalkyl or phenylalkenyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, C1-6-alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4-alkylene bridge, particularly methylene;

R^{3a} is preferably hydrogen or C1-4-alkyl;

R^4 and R^{4a} are preferably, independently hydrogen, C1-4-alkyl, phenyl or benzyl.

A further group of compounds of formula II (Compounds 1C) comprises those in racemic form wherein, when X is $-CONR^5R^6$ and R^1 is hydrogen, methyl, ethyl or propyl, then substitution on the pyrrolidine ring is other than mono-, di-, or tri-methyl or mono-ethyl.

A further group of compound of formula II (Compounds 1D) comprises those in racemic form wherein, when X is $-CONR^5R^6$ and R^1 is hydrogen or C1-6-alkyl, C2-6-alkenyl or -alkynyl or cycloalkyl, each unsubstituted, then substitution in the ring is other than by alkyl, alkenyl or alkynyl, each unsubstituted.

A further particular group of compounds of formula II (Compounds 1E) comprises those wherein,

X is -CA^{1}NH$_2$;

R^1 is H;

R^3 is azidomethyl, iodomethyl, ethyl optionally substituted by 1 to 5 halogen atoms, n-propyl optionally substituted by 1 to 5 halogen atoms, vinyl optionally subsituted by one or two methyl, and/or 1 to 3 halogen atoms, acetylene optionally substituted by C1-4-alkyl, phenyl or halogen;

R^{3a} is hydrogen or halogen, preferably fluorine;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen;

as their racemates or in enantiomerically enriched form, preferably the pure enantiomers.

A further particular group of compounds of formula II (Compounds 1F) comprises those wherein,

X is -CA^{1}NH$_2$;

R^1 is H;

R^3 is C1-6-alkyl, C2-6-alkenyl or C2-6-alkynyl optionally substituted by azido, oxynitro, 1 to 6 halogen atoms;

R^{3a} is hydrogen or halogen, preferably fluorine;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen;

as their racemates or in enantiomerically enriched form, preferably the pure enantiomers.

In all the above mentioned scopes when the carbon atom to which R^1 is attached is asymmetric it is preferably in the "S" - configuration.

The "pharmaceutically acceptable salts" according to the invention include therapeutically active, non-toxic base and acid salt forms which the compounds of formula II are able to form.

The acid addition salt form of a compound of formula II that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula II containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-

methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula II and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula II and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondance with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula II or mixtures thereof (including all possible mixtures of stereoisomers).

Furthermore certain compounds of formula II which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers.

Multiple substituents on the pyrrolidone ring can also stand in either *cis* or *trans* relationship to each other with respect to the plane of the pyrrolidone ring.

Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

The preferred active compounds of formula II are the following : (2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide ; (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide ; and (2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide.

The present invention concerns also a pharmaceutical composition for the treatment or the prevention of dyskinesia comprising a therapeutically effective amount of an active compound as described above and a pharmaceutically acceptable carrier. In particular, it also concerns a pharmaceutical composition for the treatment or prevention of movement disorders or dyskinesia comprising a therapeutically effective amount of an active compound which is (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and a pharmaceutically acceptable carrier.

The present invention requires administration of an effective dose of the active compound for the treatment and/or the prophylaxis of movement disorders or dyskinesia. The dose required in accordance with the invention should be sufficiently high to permit the relief of movement disorders or dyskinesia. Pharmaceutical compositions comprising the active compound can, for example, be administered orally or parenterally, i.e., intravenously, intramuscularly or subcutaneously, intrathecally.

Pharmaceutical compositions which can be used for oral administration can be solids or liquids and can, for example, be in the form of tablets, pills, dragees, gelatin capsules, solutions, syrups, and the like.

To this end, the active compound can be used mixed with an inert diluent or a non-toxic pharmaceutically acceptable vehicle such as starch or lactose, for example. Optionally, these pharmaceutical compositions can also contain a binder such as microcrystalline cellulose, gum tragacanth or gelatine, a disintegrant such as alginic acid, a lubricant such as magnesium stearate, a glidant such as colloidal silicon dioxide, a sweetener such as sucrose or saccharin, or colouring agents or a flavouring agent such as peppermint or methyl salicylate. They also comprise compositions which can release the active substance in a controlled manner. Pharmaceutical compositions which can be used for parenteral administration are in the pharmaceutical forms which are known for this mode of administration and are in the form of aqueous or oily solutions or suspensions generally contained in ampoules, disposable syringes, glass or plastics vials or infusion containers.

In addition to the active compound, these solutions or suspensions can optionally also contain a sterile diluent such as water for injection, a physiologic saline solution, oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as benzyl alcohol, antioxidants such as ascorbic acid or sodium bisulphite, chelating agents such as ethylene diamine-tetra-acetic acid, buffers such as acetates, citrates or phosphates and agents for adjusting the osmolarity, such as sodium chloride or dextrose.

These pharmaceutical forms are prepared using methods which are routinely used by pharmacists.

The percentage of active material in the pharmaceutical compositions can fall within a wide range of concentrations and depends on a variety of factors such as the patient's sex, age, weight and medical condition, as well as on the method of administration. Thus the quantity of active product in compositions for oral administration is at least 0.5% by weight and can be up to 80% by weight with respect to the composition weight.

In compositions for parenteral administration, the quantity of active material present is at least 0.5% by weight and can be up to 33% by weight with respect to the composition weight. For the preferred parenteral compositions, the dosage unit is in the range 0.5 mg to 5.000 mg of active product.

The daily dose can fall within a wide range of dosage units of active product, and is generally in the range of 0.01 to 100 mg/kilogram (kg). However, it should be understood that the specific doses can be adapted to particular cases depending on the individual requirements, at the physician's discretion.

The present invention concerns also a use of the pharmaceutical composition, described above, for the treatment of a patient suffering from a disease chosen among Huntington's disease, Parkinson's disease, and Schizophrenia, or for the treatment of patients exposed to chronic dopamine replacement therapy, or to chronic treatment with neuroleptics.

An active compound having formula II or the compound (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide obviate or mitigate dyskinesia when used as a monotherapy or given in combination with other treatments which also reduce dyskinesia (e.g. μ-opioid receptor antagonists , alpha2-adrenoceptor-antagonists , cannabinoid CB1-antagonists , NMDA receptor antagonists , adenosine A2a antagonists , H3- histamine receptor agonists , metabotropic Glutamate receptors antagonists , GPi lesion/deep brain stimulation).

Therefore, the present invention relates also to a pharmaceutical composition comprising an active compound which is a 2-oxo-1-pyrrolidine derivatives having the formula II or a pharmaceutically acceptable salt thereof, or the compound (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide, and at least one compound having anti-dyskinesia activity.

In another embodiment, the present invention relates to the use of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide for a manufacture of a medicament for treatment or prophylaxis of Parkinson's disease.

The present invention concerns also a pharmaceutical composition for the treatment of Parkinson's disease comprising a therapeutically effective amount of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and a pharmaceutically acceptable carrier.

The present invention concerns also a pharmaceutical composition comprising (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and at least one compound having anti-parkinsonian activity. Examples of compounds having anti-parkinsonian activity are dopamine replacing agents (e.g. L-DOPA or dopamine agonists), anticholinergic drugs, amantadine, monoamine oxidase inhibitors. A particular example of the said compound is ropinirole.

The present invention relates to a method of selectively potentiating the therapeutic effect of a compound having anti-parkinsonian activity without increasing undesired side effects associated therewith which comprises co-administration of an amount of the said compound with an amount of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide effective in producing the desired therapeutic effect.

The following examples illustrate the invention without in any way limiting its scope.

Example 1

This study was designed to investigate whether levetiracetam has anti-dyskinetic activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) - lesioned marmoset model of Parkinson's disease. The effect of levetiracetam on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias and alleviation of parkinsonism symptoms was investigated.

The study was performed on seven adult marmosets *(Callithrix jacchus)* bred in a closed colony. The marmosets were rendered parkinsonian by subcutaneous injection of 2mg/kg MPTP for 5 consecutive days. The marmosets were allowed to recover for 18 weeks until their parkinsonism became stable. The degree of activity and disability before and after MPTP treatment was assessed using a combination of scales that measure locomotor activity, mobility, bradykinesia and posture. Animals were treated with L-DOPA (12.5 mg/kg b.i.d. for 6 weeks) to prime them to elicit dyskinesia. After this time all animals demonstrated stable levels of dyskinesia when challenged with L-DOPA.

All drugs were administered orally in a volume of 5 ml/kg via a syringe in the animal's home cage. The animals were immediately transferred to the experimental cage (60cm x 55cm x 75cm, with the perch 25cm from floor of cage) for behavioural assessment. Vehicle was apple juice in all cases.

A battery of behavioural tests were performed:

1) Activity - a quantitative assessment of the amount of movement of the animal was obtained every 5 minutes for the duration of the experiment using computer-based activity monitors.

2) Parkinsonian disability - non-parametric measures based on the following scales

a) Range of movement score: 0 = no movement, 1= movement of head on the floor of the cage, 2 = movement of limbs, but no locomotion, on the floor of the cage, 3 = movement of head or trunk on wall of cage or perch, 4 = movement of limbs, but no locomotion, on wall of cage or perch, 5 = walking around floor of cage or eating from hopper on floor, 6 = hopping on floor of cage, 7 = climbing onto wall of cage or perch, 8 = climbing up and down the walls of the cage or along perch, 9 = running, jumping, climbing between cage walls / perch / roof, uses limbs through a wide range of motion and activity.

b) Bradykinesia score: 0 = normal speed and initiation of movement, 1 = mild slowing of movement, 2 = moderate slowing, difficulty initiating and maintaining movement, marked freezing, 3 = akinetic, unable to move, with prolonged freezing episodes

c) Postural abnormality score: 0 = normal, upright, holds head up, normal balance,1 = abnormal, crouched, face down, may lose balance.

d) Parkinsonian disability score: A combination of the mobility, bradykinesia and posture scores according to the formula [18 - (Range of movement * 2) + (Bradykinesia * 3) + (posture * 9)] to give a global parkinsonian disability rating.

3)Dyskinesia - non-parametric measures based on the following scale

Dyskinesia score: 0 = Absent, 1 = Mild, fleeting, 2 = Moderate, not interfering with normal activity, 3 = Marked, at times interfering with normal activity, 4 = Severe, continuous, replacing normal activity.

Behaviour was assessed for 6 hours post drug administration. Behavioural test 1, activity, was assessed every 5 minutes for 6 hours post drug administration. Behavioural tests 2 and 3, parkinsonian disability and dyskinesia, respectively, were assessed for 10 minutes every 30 minutes over the course of 6 hours, by *post hoc* analysis of video-recordings by an observer blinded to the treatment. The score given in each 10 minutes time period represents the maximum score achieved during that time period.

Table 1 outlines the randomised treatment schedule i.e. three doses of levetiracetam drug in combination with a single dose of L-DOPA. The actions of each of these three combination therapies were compared with that of L-DOPA plus the appropriate vehicle. Thus, a total of four treatments were given.

Table 1 – Randomised treatment schedule

Date / animal number

	1	2	3	4	5	6	7
Day 1	V	D1	D2	D1	D2	D3	V
Day 4	D1	D3	V	D3	V	D2	D3
Day 6	D3	D2	D1	D2	D1	V	D1
Day 8	D2	V	D3	V	D3	D1	D2

V = L-DOPA + vehicle

D1= L-DOPA (12mg/kg) + levetiracetam (13mg/kg)

D2 = L-DOPA (12mg/kg) + levetiracetam (30mg/kg)

D3 = L-DOPA (12mg/kg) + levetiracetam (60mg/kg)

L-DOPA (12mg/kg) alone reversed parkinsonian symptoms. The alleviation of parkinsonian symptoms was accompanied by severe dyskinesia.

Dyskinesia was significantly reduced following the combined treatment for the first hour post drug administration ($p < 0.01$, $p < 0.05$ and $p < 0.01$ for 13mg/kg, 30mg/kg and 60mg/kg, respectively; Friedman test followed by Dunn's multiple comparison's test). In contrast, there were no significant differences in disability scores for the first hour post drug administration ($p > 0.05$ for 13mg/kg, 30mg/kg and 60mg/kg; Friedman test followed by Dunn's multiple comparison's test). Co-administration of levetiracetam (13 to 60 mg/kg) and L-DOPA (12mg/kg) reversed parkinsonian symptoms to the same magnitude, at peak effect, as L-DOPA (12mg/kg) monotherapy. There were no significant differences in dyskinesia or disability scores at any time-point after one hour post drug administration ($p > 0.05$ for 13mg/kg, 30mg/kg and 60mg/kg; Friedman test followed by Dunn's multiple comparison's test).

Combined levetiracetam (13-60mg/kg) and L-DOPA (12mg/kg) treatment had the same maximal anti-parkinsonian action compared to L-DOPA monotherapy.

Combined levetiracetam (13-60mg/kg) and L-DOPA (12mg/kg) treatment was associated with less significantly dyskinesia, during the first hour post drug administration, than L-DOPA monotherapy.

In combination with L-DOPA, levetiracetam had a significant advantage over L-DOPA monotherapy.

The major benefit of levetiracetam was a reduction in L-DOPA-induced dyskinesia during the first hour post drug administration. This reduction in dyskinesia was seen without a reduction in anti-parkinsonian efficacy.

Thus, the clinical beneficit for levetiracetam may be as an adjunctive therapy to reduce dyskinesia in parkinson patients exposed to chronic dopamine replacement therapy, in schizophrenia patients exposed to chronic neuroleptic treatment and in patients with Huntington 's disease.

Example 2

This study was designed to investigate whether the compound ((2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide) (named compound A) has anti-dyskinetic activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) - lesioned marmoset model of Parkinson's disease. The effect of the compound A on L-3,4-dihydroxyphenylalanine (L- DOPA)-induced dyskinesias and alleviation of anti parkinsonism symptoms was investigated.

The study was performed on nine adult marmosets *(Callithrix jacchus)* bred in a closed colony. The marmosets were rendered parkinsonian by subcutaneous injection of 2mg/kg MPTP for 5 consecutive days. The marmosets were allowed to recover for 18 weeks until their parkinsonism became stable. The degree of activity and disability before and after MPTP treatment was assessed using a combination of scales that measure locomotor activity, mobility, bradykinesia and posture. Animals were treated with L-DOPA (13.9+/-0.8mg/kg b.i.d. for 6 weeks) to prime them to elicit dyskinesia. After this time all animals demonstrated stable levels of dyskinesia when challenged with L-DOPA .

All drugs were administered orally in a volume of 5 ml/kg via a syringe in the animal's home cage. The animals were immediately transferred to the experimental cage (60cm x 55cm x 75cm, with the perch 25cm from floor of cage) for behavioural assessment. Vehicle was apple juice in all cases.

A battery of behavioural tests were performed:

1) Activity - a quantitative assessment of the amount of movement of the animal was obtained every 5 minutes for the duration of the experiment using computer-based activity monitors.

2) Parkinsonian disability - non-parametric measures based on the following scales

a) Range of movement score: 0 = no movement, 1= movement of head on the floor of the cage, 2 = movement of limbs, but no locomotion, on the floor of the cage, 3 = movement of head or trunk on wall of cage or perch, 4 = movement of limbs, but no locomotion, on wall of cage or perch, 5 = walking around floor of cage or eating from hopper on floor, 6 = hopping on floor of cage, 7 = climbing onto wall of cage or perch, 8 = climbing up and down the walls of the cage or along perch, 9 = running, jumping, climbing between cage walls / perch / roof, uses limbs through a wide range of motion and activity.

b) Bradykinesia score: 0 = normal speed and initiation of movement, 1 = mild slowing of movement, 2 = moderate slowing, difficulty initiating and maintaining movement, marked freezing, 3 = akinetic, unable to move, with prolonged freezing episodes

c) Postural abnormality score: 0 = normal, upright, holds head up, normal balance,1 = abnormal, crouched, face down, may lose balance.

d) Parkinsonian disability score: A combination of the mobility, bradykinesia and posture scores according to the formula [18 - (Range of movement * 2) + (Bradykinesia * 3) + (posture * 9)] to give a global parkinsonian disability rating.

3)Dyskinesia - non-parametric measures based on the following scale

Dyskinesia score: 0 = Absent, 1 = Mild, fleeting, 2 = Moderate, not interfering with normal activity, 3 = Marked, at times interfering with normal activity, 4 = Severe, continuous, replacing normal activity.

Behaviour was assessed for 6 hours post drug administration. Behavioural test 1, activity, was assessed every 5 minutes for 6 hours post drug administration. Behavioural tests 2 and 3, parkinsonian disability and dyskinesia, respectively, were assessed for 10 minutes every 30 minutes over the course of 6 hours, by *post hoc* analysis of video-recordings by an observer blinded to the treatment. The score given in each 10 minutes time period represents the maximum score achieved during that time period.

Four doses of compound A drug (1mg/kg , 3mg/kg , 10mg/kg and 30mg/kg) in combination with a single dose of L-DOPA were tested using a randomized treatment schedule. The actions of each of these four combination therapies were compared with that of L-DOPA plus the appropriate vehicle. Thus, a total of five treatments were given.

L-DOPA alone reversed parkinsonian symptoms. The alleviation of parkinsonian symptoms was accompanied by dyskinesia.

At the doses of 10mg/kg and 30mg/kg of compound A, dyskinesia was significantly reduced following the combined treatment with L-DOPA for the first hour post drug administration ($p>0.05$ for 1mg/kg and 3mg/kg , $p<0.05$ for 10mg/kg and 30mg/kg ; Friedman test followed by Dunn's multiple comparison's test). In contrast, there were no significant differences in disability scores for the first hour post drug administration ($p > 0.05$ for 1mg/kg, 3mg/kg , 10mg/kg and 30mg/kg; Friedman test followed by Dunn's multiple comparison's test).

Co-administration of compound A (1 to 30 mg/kg) and L-DOPA (13.9+/-0.8mg/kg) reversed parkinsonian symptoms to the same magnitude, at peak effect, as L-DOPA (13.9+/-0.8mg/kg) monotherapy. There were no significant differences in dyskinesia or disability scores at any time-point after one hour post drug administration ($p > 0.05$ for 1mg/kg, 3mg/kg , 10mg/kg and 30mg/kg; Friedman test followed by Dunn's multiple comparison's test).

Combined compound A (1-30mg/kg) and L-DOPA (13.9+/-0.8mg/kg) treatment had the same maximal anti-parkinsonian action compared to L-DOPA monotherapy.

Combined compound A (10 and 30mg/kg) and L-DOPA (13.9+/-0.8mg/kg) treatment was associated with less significantly dyskinesia, during the first hour post drug administration, than L-DOPA monotherapy.

In combination with L-DOPA, compound A had a significant advantage over L-DOPA monotherapy.

The major benefit of compound A was a reduction in L-DOPA-induced dyskinesia during the first hour post drug administration. This reduction in dyskinesia was seen without a reduction in anti-parkinsonian efficacy.

Thus, the clinical beneficit for compound A may be as an adjunctive therapy to reduce dyskinesia in parkinson patients exposed to chronic dopamine replacement therapy, in schizophrenia patients exposed to chronic neuroleptic treatment and in patients with Huntington 's disease.

Example 3

This study was designed to investigate whether Levetiracetam has a potential as an adjunctive anti-parkinsonian agent to dopamine replacement therapy in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease. The effect of Levetiracetam on Ropinirole alleviation of parkinsonism symptoms was investigated.

The study was performed on six adult marmosets (*Callithrix jacchus;* 4 female, 2 male). The marmosets were rendered parkinsonian by subcutaneous injection of 2mg/kg MPTP for 5 consecutive days. The marmosets were allowed to recover for 18 weeks until their parkinsonism was stable. The degree of activity and disability before and after MPTP treatment were assessed using a combination of scales that measure locomotor activity, mobility, bradykinesia and posture. Animals were treated with L-DOPA 12mg/kg b.i.d. for 6 weeks. After this time, animals were used for assessment of potential symptomatic antiparkinsonian therapy. All drugs were administered orally in a volume of 5 ml/kg via a syringe in the animal's home cage. The animals were immediately transferred to an experimental cage (60cm x 55cm x 75cm, with the perch 25cm from floor of cage) for behavioural assessment. Vehicle was apple juice in all cases. The doses were 3.75 mg/kg of Ropinirole in combination with Levetiracetam at 13, 30 and 60 mg/kg. Behaviour was assessed for 6 hours post drug administration.

A battery of behavioural tests was performed:

1) Activity -a quantitative assessment using computer-based activity monitors was obtained every 5 minutes for the duration of the experiment.

2) Parkinsonian disability -non-parametric measures based on the following scales:

a) Range of movement score: 0 = no movement, 1 = movement of head on the floor of the cage, 2 = movement of limbs, but no locomotion, on the floor of the cage, 3 = movement of head or trunk on wall of cage or perch, 4 = movement of limbs, but no locomotion, on wall of cage or perch, 5 = walking around floor of cage or eating from hopper on floor, 6 = hopping on floor of cage, 7 = climbing onto wall of cage or perch, 8 = climbing up and down the walls

of the cage or along perch, 9 = running, jumping, climbing between cage walls / perch / roof, uses limbs through a wide range of motion and activity. The score given was the maximum achieved in each 10 minute observation period.

b) Bradykinesia score: 0 = normal speed and initiation of movement, 1 = mild slowing of movement, 2 = moderate slowing, difficulty initiating and maintaining movement, marked freezing, 3 = akinetic, unable to move, with prolonged freezing episodes. The score given was representative of behaviour over the observation period.

c) Postural abnormality score: 0 = normal, upright, holds head up, normal balance, 1 = abnormal, crouched, face down, may lose balance. The score given was representative of behaviour over the observation period.

d) Parkinsonian disability score: A combination of the mobility, bradykinesia and posture scores according to the formula [18 - (Range of movement * 2) + (Bradykinesia * 3) + (Posture * 9)] to give a global parkinsonian disability rating.

Behavioural test 1 (activity) was assessed every 5 minutes for 6 hours post drug administration. Behavioural tests 2 (parkinsonian disability) was assessed for 10 minutes every 30 minutes over the course of 6 hours, by *post hoc* analysis of video-recordings by an observer blinded to the treatment. The score given / achieved in each 10 minute time period was presented.

Range of movement score: 0 = none, 3 = low, 6 = moderate, 9 = high

Bradykinesia score: 0 = none, 1 = mild, 2 = moderate, 3 = severe

Postural abnormality score: 0 = none, 0.5 = mild, 1 = severe

Parkinsonian disability score: 0 = none, 9 = mild, 18 = moderate, 27 = marked, 36 = severe

Cumulated data for parkinsonian disability, range of movement, bradykinesia and postural abnormalities were analysed with a non-parametric repeated measures one-way ANOVA (Friedman's test) followed by Dunn's multiple comparison test (Graphpad Prism version 3).

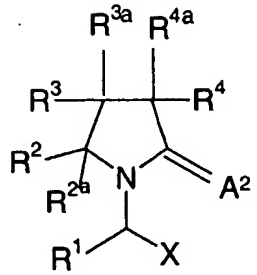
Levetiracetam, administered at 13 and 30mg/kg but not 60 mg/kg, significantly potentiated the alleviation of parkinsonism by Ropinirole (3.75mg/kg). Thus, Levetiracetam, administered at 13 and 30mg/kg significantly increased activity and "on-time" (all $P < 0.01$; one-way repeated measures ANOVA followed by Dunnett's multiple comparison's test). Also, Levetiracetam administered at 13mg/kg significantly reduced parkinsonian disability over the experiment as a whole and specifically during 3-4 hour time period ($P < 0.05$; Friedman's test followed by Dunn's multiple comparison's test). Furthermore, Levetiracetam, administered at 30mg/kg, significantly increased range of movement during the 0-1 hour time period ($P < 0.05$; Friedman's test followed by Dunn's multiple comparison's test). In conclusion , the increase in general activity levels was accompanied by a significant

reduction in parkinsonian disability and reflects an enhancement of the anti-parkinsonian actions afforded by Ropinirole. Furthermore, there was an enhancement of "on-time" by approximately 82% and 69% for 13mg/kg and 30mg/kg Levetiracetam, respectively. However, activity counts were still elevated at the end of the six hour experiment suggesting that observed "on-time" might have been greater if the experiment had not been terminated at six hours.

Levetiracetam may have potential as an anti-parkinsonian agent in combination with dopamine replacement therapy. The extension of "on-time" might represent a useful *de novo* therapy to delay the onset of dyskinesia.

CLAIMS

1. Use of an 2-oxo-1-pyrrolidine derivative having the formula II or a pharmaceutically acceptable salt thereof,



(II)

wherein

X is $-CA^1NR^5R^6$ or $-CA^1OR^7$ or $-CA^1-R^8$ or CN;

A^1 and A^2 are independently oxygen, sulfur or $-NR^9$;

R^1 is hydrogen, alkyl, aryl or $-CH_2-R^{1a}$ wherein R^{1a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R^2, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;

R^{2a}, R^{3a} and R^{4a} are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;

R^5, R^6, $R^7$and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

with the provisos that at least one of as R^2, R^3, R^4, R^{2a}, R^{3a} and R^{4a} is other than hydrogen; and that when the compound is a mixture of all possible isomers , X is $-CONR^5R^6$, A^2 is oxygen and R^1 is hydrogen, methyl, ethyl or propyl then substitution on the pyrollidine ring is other than mono-, di-, or tri-methyl or mono-ethyl; and that when R^1, R^2, R^4, R^{2a}, R^{3a} and R^{4a} are each hydrogen, A^2 is oxygen and X is $CONR^5R^6$ then R^3 is

different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by an halogen atom;
for the manufacture of a medicament for treatment or prophylaxis of dyskinesia.

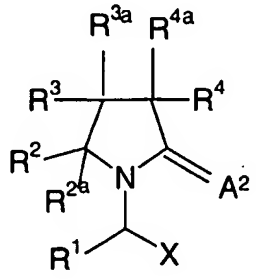
2. Use of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the manufacture of a medicament for treatment or prophylaxis of movement disorders or dyskinesia.

3. Use of (2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide for the manufacture of a medicament for treatment or prophylaxis of dyskinesia.

4. Use of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide for the manufacture of a medicament for treatment or prophylaxis of dyskinesia.

5. Use of (2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide for the manufacture of a medicament for treatment or prophylaxis of dyskinesia.

6. Method for treating or preventing dyskinesia, comprising administering a therapeutic amount of an active compound which is an 2-oxo-1-pyrrolidine derivative having the formula II or a pharmaceutically acceptable salt thereof,



(II)

wherein
X is $-CA^1NR^5R^6$ or $-CA^1OR^7$ or $-CA^1-R^8$ or CN;
A^1 and A^2 are independently oxygen, sulfur or $-NR^9$;

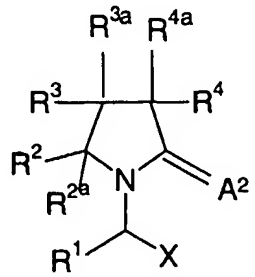
R^1 is hydrogen, alkyl, aryl or $-CH_2-R^{1a}$ wherein R^{1a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;
R^2, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;
R^{2a}, R^{3a} and R^{4a} are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;
R^5, R^6, $R^7$and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and
R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;
with the provisos that at least one of as R^2, R^3, R^4, R^{2a}, R^{3a} and R^{4a} is other than hydrogen; and that when the compound is a mixture of all possible isomers , X is $-CONR^5R^6$, A^2 is oxygen and R^1 is hydrogen, methyl, ethyl or propyl then substitution on the pyrollidine ring is other than mono-, di-, or tri-methyl or mono-ethyl; and that when R^1, R^2, R^4, R^{2a}, R^{3a} and R^{4a} are each hydrogen, A^2 is oxygen and X is $CONR^5R^6$ then R^3 is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by an halogen atom; to a patient in need.

7. Method according to claim 6, wherein the active compound is selected from the group consisting of (2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide ; (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide ; or (2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide.

8. Method for treating or preventing movement disorders or dyskinesia, comprising administering a therapeutic amount of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide to a patient in need.

9. Method according to claim 6, 7 or 8, wherein the patients are patients with Huntington's disease, Parkinson's disease patients exposed to chronic dopamine replacement therapy, or Schizophrenia patients exposed to chronic treatment with neuroleptics.

10. A pharmaceutical composition for the treatment or prevention of dyskinesia comprising a therapeutically effective amount of an active compound which is 2-oxo-1-pyrrolidine derivative having the formula II or a pharmaceutically acceptable salt thereof,



(II)

wherein

X is $-CA^1NR^5R^6$ or $-CA^1OR^7$ or $-CA^1-R^8$ or CN;

A^1 and A^2 are independently oxygen, sulfur or $-NR^9$;

R^1 is hydrogen, alkyl, aryl or $-CH_2-R^{1a}$ wherein R^{1a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R^2, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;

R^{2a}, R^{3a} and R^{4a} are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;

R^5, R^6, $R^7$and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

with the provisos that at least one of as R^2, R^3, R^4, R^{2a}, R^{3a} and R^{4a} is other than hydrogen; and that when the compound is a mixture of all possible isomers , X is $-CONR^5R^6$, A^2 is oxygen and R^1 is hydrogen, methyl, ethyl or propyl then substitution on the pyrollidine ring is other than mono-, di-, or tri-methyl or mono-ethyl; and that when R^1, R^2, R^4, R^{2a}, R^{3a} and R^{4a} are each hydrogen, A^2 is oxygen and X is $CONR^5R^6$ then R^3 is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by an halogen atom;

and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for the treatment or prevention of movement disorders or dyskinesia comprising a therapeutically effective amount of an active compound which is (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and a pharmaceutically acceptable carrier.

12. Use of a pharmaceutical composition of claim 10 or 11 for the treatment of a patient suffering from a disease chosen among Huntington's disease, Parkinson's disease, and Schizophrenia, or for the treatment of patients exposed to chronic dopamine replacement therapy, or to chronic treatment with neuroleptics.

13. A pharmaceutical composition comprising an active compound which is a 2-oxo-1-pyrrolidine derivatives having the formula II or a pharmaceutically acceptable salt thereof, according to claim 10, or the compound (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide, and at least one compound having anti-dyskinesia activity.

14. Use of (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide for a manufacture of a medicament for treatment or prophylaxis of Parkinson's disease.

15. A pharmaceutical composition comprising (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide and at least one compound having anti-parkinsonian activity, such as ropinirole.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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01123976.1 8 October 2001 (08.10.2001) EP

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(74) Agent: **LECHIEN, Monique**; UCB, S.A., Intellectual Property Department, Allée de la Recherche, 60, B-1070 Bruxelles (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
8 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF 2-OXO-1-PYRROLIDINE DERIVATIVES FOR THE TREATMENT OF DYSKINESIA AND MOVEMENT DISORDERS

(57) Abstract: The present invention relates to the use of 2-oxo-1-pyrrolidine derivatives (and in particular (S)-(-)-α-ethyl-2-oxo-1-pyrrolidineacetamide) for the preparation of drugs for the curative and/or prophylactic treatment of dyskinesia

WO 2003/030899 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4015 A61P25/16 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, CHEM ABS Data, SCISEARCH, MEDLINE, BIOSIS, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 62726 A (DIFFERDING EDMOND ;LALLEMAND BENEDICTE (BE); MATAGNE ALAIN (BE); P) 30 August 2001 (2001-08-30) claims 1,30,31,33,35 ---	1,3-10
X	GB 1 309 692 A (UCB SA) 14 March 1973 (1973-03-14) page 1, line 1 - line 24 page 3, line 21 - line 30 claim 1 ---	1,2,6-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 August 2003	13/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2. NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROSSI F. ET AL: "'Nootropic drugs!. I FARMACI NOOTROPI." RIFORMA MEDICA, (1993) 108/1 (1-14)., XP008019117 page 3, column 2, paragraph 1 figure 2 page 7, column 1, paragraph 2 -column 2, paragraph 2 page 8, column 1, paragraph 5	1,2,6-10
X	US 4 696 943 A (GOBERT JEAN ET AL) 29 September 1987 (1987-09-29) page 1, line 5 - line 15	1,2,6,8, 9
X	WO 01 39779 A (LAMBERTY YVES ;MATAGNE ALAIN (BE); UCB SA (BE); WAEGEMANS TONY (BE) 7 June 2001 (2001-06-07) page 6, paragraph 2 page 14, line 9 - line 19 page 1, line 8	1,2,6-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11203

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9, 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 13 relates to a compound defined by reference to a desirable characteristic or property, namely the activity as anti-diskinesia compound.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Present claims 1,6,9,10,12 relate to an extremely large number of possible compounds (formula II). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 2-5 and described in formula II, and to their combinations with the compound mentioned in claim 15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/11203

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0162726 A	30-08-2001	AU 5214401 A	03-09-2001
		AU 7389601 A	12-09-2001
		BG 107004 A	30-04-2003
		BG 107016 A	30-04-2003
		BR 0108657 A	29-04-2003
		BR 0108664 A	29-04-2003
		CA 2401033 A1	30-08-2001
		CA 2401048 A1	07-09-2001
		CN 1404469 T	19-03-2003
		CN 1404470 T	19-03-2003
		CZ 20022849 A3	12-02-2003
		CZ 20022850 A3	12-02-2003
		WO 0164637 A1	07-09-2001
		WO 0162726 A2	30-08-2001
		EP 1265862 A2	18-12-2002
		EP 1263727 A1	11-12-2002
		HU 0204526 A2	28-04-2003
		HU 0300196 A2	28-06-2003
		NO 20023995 A	21-10-2002
		NO 20023997 A	22-10-2002
		US 2003120080 A1	26-06-2003
		US 2003040631 A1	27-02-2003
GB 1309692 A	14-03-1973	BE 762728 A4	10-08-1971
		CH 530395 A	15-11-1972
		CS 167911 B2	28-05-1976
		CS 167912 B2	28-05-1976
		CY 727 A	01-03-1974
		DE 2106418 A1	19-08-1971
		DK 137451 B	06-03-1978
		ES 388135 A2	01-05-1973
		FI 54916 B	29-12-1978
		FR 2081508 A6	03-12-1971
		JP 53005301 B	25-02-1978
		JP 986288 C	07-02-1980
		JP 53130656 A	14-11-1978
		JP 54020491 B	23-07-1979
		MY 7274 A	31-12-1974
		NL 7101697 A ,B,	17-08-1971
		SU 508185 A3	25-03-1976
		SU 508186 A3	25-03-1976
		YU 30671 A ,B	31-10-1979
		YU 144578 A1	31-10-1982
		ZA 7100877 A	27-10-1971
US 4696943 A	29-09-1987	AT 45567 T	15-09-1989
		AU 574465 B2	07-07-1988
		AU 4253085 A	20-11-1986
		BG 47497 A3	16-07-1990
		BG 50156 A3	15-05-1992
		CA 1235129 A1	12-04-1988
		CN 85105301 A ,B	14-01-1987
		CY 1567 A	20-12-1991
		DE 3572348 D1	21-09-1989
		DK 212985 A ,B,	16-11-1985
		EP 0162036 A1	21-11-1985
		ES 8608485 A1	01-12-1986
		ES 8704893 A1	01-07-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/11203

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4696943 A		FI	851875 A ,B,	16-11-1985
		GR	851155 A1	25-11-1985
		HK	52391 A	19-07-1991
		IE	59950 B1	04-05-1994
		IL	75179 A	31-05-1988
		JP	1901367 C	27-01-1995
		JP	6029186 B	20-04-1994
		JP	60252461 A	13-12-1985
		KR	9203818 B1	15-05-1992
		LT	2584 R3	25-03-1994
		LU	90615 A9	02-10-2000
		LU	90682 A9	30-01-2001
		LV	5233 A3	10-10-1993
		NO	851933 A ,B,	18-11-1985
		PL	253374 A1	06-05-1986
		PL	257385 A1	07-10-1986
		PT	80460 A ,B	01-06-1985
		SG	80090 G	23-11-1990
		SU	1402260 A3	07-06-1988
		SU	1430392 A1	15-10-1988
		SU	1428195 A3	30-09-1988
		US	4837223 A	06-06-1989
		US	4943639 A	24-07-1990
		ZA	8503635 A	24-12-1985
WO 0139779 A	07-06-2001	AU	1524101 A	12-06-2001
		BG	106708 A	28-02-2003
		BR	0015974 A	23-07-2002
		CA	2392879 A1	07-06-2001
		CN	1402637 T	12-03-2003
		CZ	20021904 A3	13-11-2002
		EE	200200274 A	16-06-2003
		WO	0139779 A1	07-06-2001
		EP	1244456 A1	02-10-2002
		HU	0204023 A2	28-03-2003
		JP	2003515564 T	07-05-2003
		NO	20022585 A	25-07-2002